Swami Ramanand Teerth Marathwada University, Nanded, Maharashtra, India

NAAC Re-accredited 'B^{++}' grade with CGPA 2.96

TITLE OF SYNOPSIS

GREEN SYNTHESIS OF NITROGEN AND SULPHUR CONTAINING NOVEL BIOACTIVE HETEROCYLIC COMPOUNDS

Research Proposal Submitted

In Partial fulfilment of Registration to

Ph.D Programme

In the Subject of

CHEMISTRY

FACULTY OF SCIENCE AND TECHNOLOGY

Submitted by

Asma Anjum Syed Ubaidullah Daimi

Under the Supervision of

Dr. Arshia Parveen

Assistant Professor & Research Supervisor
Department of chemistry
B. Raghunath ACS College, Parbhani 431401

Year 2023-2024

Research Centre: -Shri Shivaji Mahavidiyalaya, Parbhani

SYNOPSIS

Title of the proposed research

Green Synthesis of Nitrogen and Sulphur Containing Novel Bioactive Heterocyclic Compounds

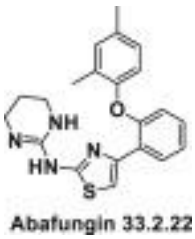
Abstract:-

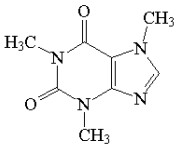
The concept of green chemistry has made significant impact on many frontages including the use of green solvents, bio-renewable resources and sustainable catalyst materials Environmentally benign protocols have been explored for heterocyclic synthesis to improve energy consumption, atom economy and reaction yields. Designing the high efficiency reactions that work at room temperature and use of alternative energy sources has become an attractive choice. Heterocycles have constituted one of the largest areas of research in organic chemistry. Nearly 80% of medications used in clinical settings have a heterocyclic composition. Green chemistry is the universally term to describe the movement towards more environmentally acceptable, chemical processes and products. Green chemistry can achieve these objectives by applying environment friendly technologies. With the increasing economic and environmental concerns, problems faced by chemical and pharmaceutical industries therefore the development of environmentally benign and inexpensive protocols has become very demanding. The substituted heterocyclic nuclei such as pyrrole, quinazoline, Substituted Piperazine, Pyrimidine, benzothiazole etc are in combination enhances the biological profile many fold than parent nuclei. Number of naturally occurring and synthetic molecules with attractive biological activities such as antiviral, anticancer, antibacterial, antifungal, anticonvulsant, and anti-inflammatory activities.

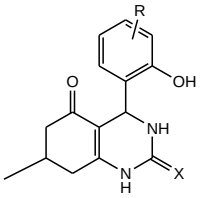
Introduction: green chemistry has made significant impact Heterocycles play on important role in biochemistry processes because the side groups of the most typical and essential constituents of living cells, DNA and RNA are based on aromatics heterocycles [1],Heterocyclic moiety is found as a key structural element in a number of therapeutic medication categories, including analgesic, anti-convulsant, anti-inflammatory, anti-hypertensive, anti-malarial, anti-depressant, anti-histaminic, anti-proliferative, and antidiabeticetc [2]. Along with multistep synthesis, synthesis via one pot or Multicomponant reactions (MCRs) have also gain substantial scope due to powerful bond forming effectiveness in combinatorial and medicinal chemistry [3].Heterocycles are completely interlinked into the life processes. Among the heterocycles, the pyrrole, quinoxaline, pyrazole, Piperazine, Substituted Piperazine and Pyrimidine occupy a prominent position. [4,5].Heterocyclic compounds are the cyclic organic compounds which contain at least one hetero atom, the most common heteroatom's are the nitrogen, oxygen and Sulphur atoms are widely known[6,7].Medicinal chemistry is the science that deals with the discovery and design of new therapeutic chemicals and their development into useful medicines [8, 9].

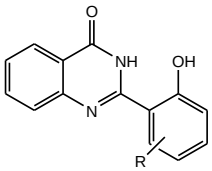
Literature Survey:

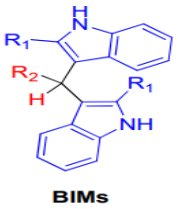
From the literature survey it is observed that, the many heterocyclic compounds are shows antiproliferative activity to different degrees, it's difficult to predict which combination of group acts on which type of target [10, 11]. Prediction about their activity is difficult, in present time there is lot of research is happening on anticancer agents, basically we have to treat the kinases /enzymes in the body for the effective treatment of cancer [12, 13]. Presently all the research is focused on different kinases as these plays a key role in the cancer metabolism and functions of normal body cells [14]. The analogs of nitrogen and sulfur based heterocycles occupy an exclusive position as a valuable source of therapeutic agents in medicinal chemistry. More than 75% of drugs approved by the FDA and currently available in the market are nitrogen and sulfur containing heterocyclic moieties [1 to 10]. Heterocyclic nuclei offer a huge area for new lead molecules for drug discovery and for generation of activity relationships with biological targets for enhance pharmacological effects. Below some drugs related to above introduction.











Antifungal Antitubercular drug Antibacteral Antiviral Antimocrobial

Aims and Objectives of the research:

The main objectives of the proposed work include,

1. To synthesize by using green methods new series of nitrogen and Sulphur containing Benzthaizole, thaizole pyrimidine and pyridine heterocycles.
2. To characterize newly synthesized compounds by modern spectral techniques
3. Biological testing such as antibacterial, antifungal, antiviral, antiproliferative activity and kinase study of synthesized compounds.

Hypothesis:

Literature search and design of bioactive molecules. To synthesize of designed analogues, having different combinations of heterocycles. Antimicrobial, Antiviral, Antifungal, Antiproliferative and kinase activity testing of designed molecules.

Methodology:

The focus of green chemistry lies on reducing environmental pollution by designing benign reaction processes, avoiding waste generation and saving time and energy. Considering the objectives synthesis of target molecule will be carried out with different starting materials such as Benzthaizole, pyridine, pyrimidine substituted piperazine etc, through a series of reactions and their sulphonamide, amide and acetamide derivative. Attempt will be made to optimize existing methodology or to develop new method for synthesis of series. The synthesized compounds of above class will be then tested for related biological activity using in-vitro assay. The techniques like UV, IR, 1H NMR, 13C NMR Spectroscopy will be used for the structural determination of the synthesized compounds.

Need and significance:

The different heterocyclic derivative possesses different biological activity it's difficult to predict which combination groups acts on which diseases, so regular research is needed. The development in chemotherapy of synthetic drugs totally depends upon the biological results of chemotherapeutic agents which ultimately give the guidelines to the research workers in selection of agents for further clinical studies and set the pattern of future drug evaluation. Considering literature survey, the fusion of two or more heterocyclic nuclei such as thiazole, benzthiazole pyridine, pyrimidine indazole Piperazine, etc are in combination enhances the biological profile many fold than parent nuclei. Number of naturally occurring and synthetic molecules with attractive biological activities such as antiviral, anticancer, antibacterial, antifungal, anticonvulsant, and anti-inflammatory activities that is well illustrated by the large number of drugs in the market containing this heterocyclic moiety.

Proposed Work Plan:-

First Year: -

1. Reactions in water

1.1 A novel and direct method for the synthesis of pharmacologically promising spiro[indoline-3,7′-pyrrolo[1,2-*c*] imidazole]-6′-carbonitrile derivatives has been developed via a three-component one pot reaction reaction. The reaction was cleaner and proceeded in good yields using isatin, malononitrile, and hydantoin or thiohydantoin in the presence of Et3N/water (Figure 1) [13].

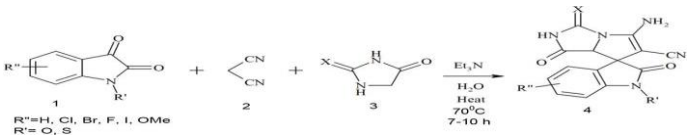
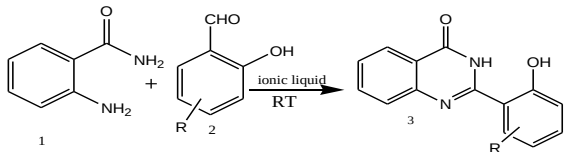


Figure 1 Synthesis of spiro[indoline-3,7′-pyrrolo[1,2-c]imidazole]-6′-carbonitrile derivatives

1.2 Synthesis of 2-(2-Hydroxyphenyl) quinazoline-4(3H)-one



Second Year:-

1.3 Synthesis of Octahydroquinazolinones Derivatives

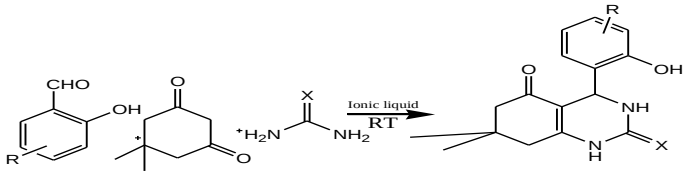


Figure 3. pyrazole-3-carboxylates

2. Mechanostic Synthesis:-

2.1 Synthesis of bis(indolyl)methanes: Mechanochemically promoted organic reactions have shown considerable attention due to their advantages of high reaction rates and solventless procedures. Bis(indolyl)methanes (BIMs) have been attractive targets to develop green methodologies because of their wide range of biological, industrial and synthetic applications. These compounds have proven to be of importance as they exhibit anticancer and antimicrobial activities.

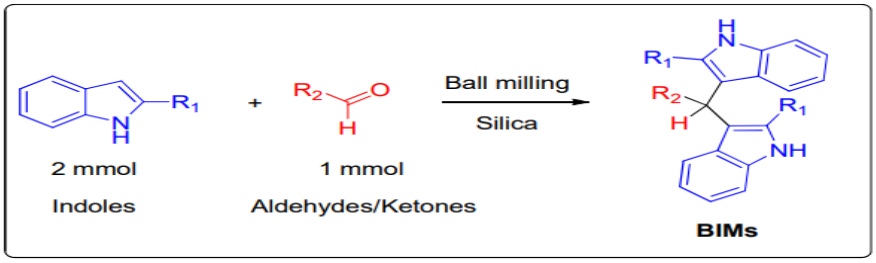
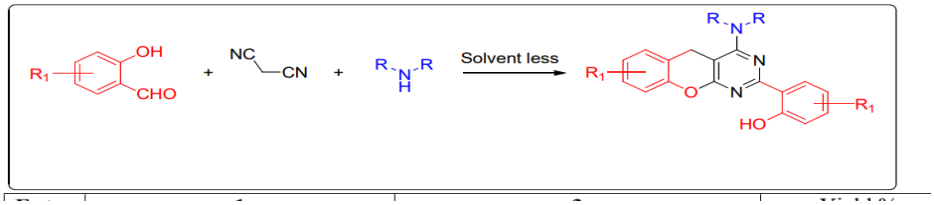


Figure 4 Synthesis of bis(indolyl)methanes (BIMs)

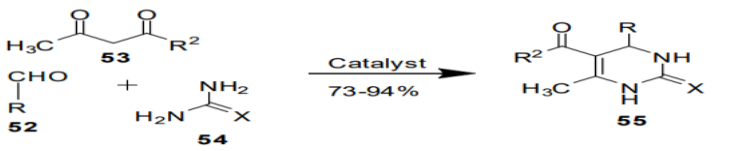
2.2 Solvent less Synthesis of Chromeno[2,3-d]pyrimidines

As a part of our research to develop green approaches to biologically relevant molecules we were interested in synthesizing Benzopyrano[2,3-d]pyrimidine. A solvent free, catalyst free protocol for the synthesis Chromeno[2,3-d]pyrimidines.



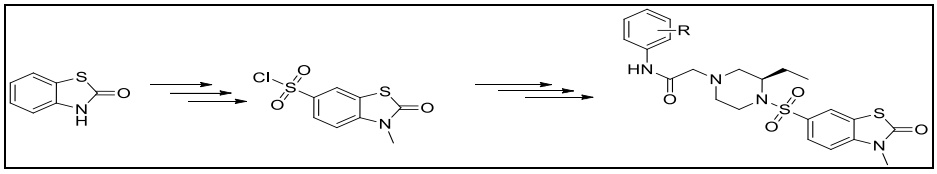
Third Year:-

2.3 The preparation of 3, 4- dihydropyrimidine. The same group has also reported54 the one-pot condensation reactions of aldehydes, β-keto esters, and urea or thiourea using environmentally friendly catalyst.



R = Aryl, Alkyl R^2= OEt, OMe X = O, S

2.4 Synthesis of Piperazine substituted Benzthaizole derivatives.



Complete characterization and Antimicrobial of bioactive study will carry out.

Preliminary Bibliography:

[1] a) Joule, J. A.; Mills, K. Heterocyclic Chemistry, 4thed. Blackwell, 369; 2000
b) Yadav, P. S.; Devpraksh and Senthilkumar, G. P. Inter. J. Pharm. Sci. Drug Res. 2011, 3(1),

[2] Tao-Qian Zhao ,Zhong-Hua Li, ,Xue-Qi Liu,. *Eur.J.Med.Chem*.2018,(143), 1396-1405

[3] Venkatesh R, Kasabonia S, Bidayat D, Kumar N U. Jain N, *Bio-org & Med. Chem. Lett*. 2017, 27, 354-359.

[4] Zhu, J., Bienayme, H., Eds.; Wiely-VCH: Wenham, 2005;
a. Do, H.-Q.; Daugulis, O. J. Am. Chem. Soc. 2007, 129, 12404.b.Saini, M.S.; Kumar, A.; Dwivedi, J.; Singh, R. A review: Biological significances of heterocyclic compounds. Int. J. Pharm. Sci. Res. 2013, 4, 66–77.

[5] a)Vinsova, J.; Horak, V.; Buchta, V.; Kaustova, J. Molecules 2005, 10, 783.b)Daidone, G.; Maggio, B.; Schillari, Salicylanilide and its heterocyclic analogs. A comparative study of their antimicrobial activity. D. Pharmazie 1990, 45, 441.

[6] a) Gududuru,V,Hurh, H.Dalton,J. T.Miller,.Synthesis and antiproliferative activity of 2-aryl-4- oxo-thiazolidin-3-yl-amides for prostate cancer, Bioorg. Med. Chem.Lett.2004, 14 (21), 5289-5293. b) Evindar, G.; Batey, R. A. J. Org. Chem. 2006, 71, 1802.

[7] a) Maradolla, M. B.; Allam, S. K.; Mandha, A.; Chandramouli, G. V. P. Arkivoc 2008, XV, 42
b)H.Kaur, S. Kumar, I. Singh, K. K. Saxena, and A. Kumar, "Synthesis, characterization and biological activity of various substituted benzothiazole derivatives," Digest Journal of Nanomaterials& Biostructures, vol. 5, no. 1, pp. 67–76, 2010

[8] Nagarjukerru, shreekanta.B.A Review on Recent Advances in Nitrogen-Containing Molecules and Their Biological Applications. Molecules 2020, 25(8), 1909

[9] H. P. Singh, C. S. Sharma, and C. P. Gautam, "Synthesis and pharmacological screening of some novel 2-arylhydrazino and 2-aryloxy-pyrimido [2,1-b] benzothiazole derivatives," American-Eurasian Journal of Scientific Research, vol. 4, no. 4, pp. 222–228, 2009.

[10] Praveen K. Sharma1,* Andleeb Amin1 and M. Kumar, Medicinally Important Nitrogen Sulphur Containing Heterocycles, The Open Medicinal Chemistry Journal, 2020, Volume 14 51.

[11] Moghaddam, F. M.; Bardajee, G. R.; Ismaili, H.; Taimoory, S. M. D. Syn. Commun. 2006, 36, 2543.

[12] . a) Kangani, C. O.; Kelley, D. E.; Day, B. W. Tetrahedron Lett. 2006, 47, 6497. b) Ayati, S. Emami, Asadipour, A. Shafiee, Eur. J. Med. Chem., 2015, 97, 699-718.

[13] I. G. Shahin, N. S. Abutaleb, M. Alhashimi, A. E. Kassab, K. O. Mohamed, A. T. Taher, M. N. Seleem, A. S. Mayhoub, Eur. J. Med. Chem., 2020, 112497.
[14] P. C. Sharma, K. K. Bansal, A. Sharma, D. Sharma, A. Deep, Thiazole-containing compounds as therapeutic targets for cancer therapy, Eur. J. Med. Chem.,2020, 188, 112016.
[15] Sengupta A K and Gupta A A, J. Antibact. Antifungal agent JPN, 1980, 8, 7.
[16] Molnar-Kimber K, Yonno L, Hearlip R and Weichman, Agents actions. 1993, 39, 677.
[17] Duplantier A J and Cherg J B, Ann. Rep. Med. Chem. 1994, 29, 73.
[18] Prous I R, Ed., Drugs Future, 1993, 18, 475.
[19] Seth P K and Parwar S S, Can J Pharmacol. 1965, 43, 1019.
[20] Chem Abstr. 1968, 68, 2195.
[21] Shetty B V, US Pat, 1970, 3, 549, 634; Chem Abstr. 1971, 75, 5940.
[22] Otto H and Houlohan W W, Swiss Pat. 1971, 459, 544; Chem Abstr. 1971, 75, 20435.
[23] Handfmann G E, US Pat. 1971, 3, 563, 990. Chem. Abstr. 1971, 75, 5930.
[24] Pandey V K, Lohani H C, Shanker K and Dovel D C, Indian Drugs, 1983, 20, 315.
[25] Pandey V K, Mishra D and Sukla S, Indian Drugs, 1994, 31, 532.
[26] Pandey V K, Indian Drugs, 1988, 26, 168.
[27] Pandey V K, Gupta M and Mishra D, Indian Drugs, 1996, 33, 409.
[28] Pandey V K, Pathak L P and Mishra S K, Indian J. Chem., 2005, 44, 1940.
[29] Vogel A I, A Text Book Quantitative Inorganic Analysis; 3rd Ed. ELBS and Langman's Green and Co. Ltd., London. 1962.
[30] Geary W J, Coord. Chem. Rev. 1972, 1, 81.
[31] Angela Kriza, Cezar Spena and Mario Pleniceanu, J. Indian Chem. Soc., 2000, 77, 83.
[32] Halli M B and Qureshi Z S, Indian J. Chem. 2004, 43A, 2347.
[33] Cotton F A and Wilkinson G, Advanced Inorganic Chemistry; 2nd Ed. Wiley Eastern, New York, 1967.
[34] Bekhet M M and Ibrahim K M, Synth, React. Iorg. Met. Org. Chem., 1986, 16, 1135
[35] Verma J K and Verma G S P, Indian J. Chem., 1982, 21A, 825.
[36] Lever A B P, Inorganic Electronic Spectroscopy; Elsevier, New York, 1984.
[37] Sulekh Chandra and Gupta K, Indian J. Chem. 2001, 40A, 775.
[38] Underhill A E and Billing D, Nature, 1996, 210, 834.
[39] Lever A B P, Inorganic Spectroscopy, Elsevier

Research Student **Research Centre** **Research Guide**

Asma Anjum Syed Ubaidullah Daimi **Dr. Arshia Parveen**

Assistant Professor
Department of chemistry

B.Raghunath ACS College, Parbhani 431401